Could exercise unveil the mystery of non-response to cardiac resynchronization therapy?

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This editorial refers to ‘Effects of physical exercise on cardiac dyssynchrony in patients with impaired left ventricular function’ by M. Kühne et al., on page 839.

Cardiac resynchronization therapy (CRT) is an established non-pharmacological therapy for patients with advanced heart failure in the last decade.1 Although the compelling evidence from multiple clinical trials suggests that CRT improves symptoms, exercise capacity, and cardiac function as well as reduces heart failure hospitalization and cardiovascular mortality, poor or no response to CRT is observed in about one-third of patients receiving this therapy.2,3 It has been suggested that insufficient evidence of mechanical dyssynchrony before device implantation might be one of the major reasons, while others include the presence of transmural scar at posterolateral wall, lack of myocardial contractile reserve, severe mitral regurgitation, suboptimal left ventricular (LV) lead position, and inappropriate device programming.2,4,5

Left ventricular mechanical dyssynchrony describes the differences in the timing of contraction between different myocardial segments that are commonly observed in patients with congestive heart failure, particularly in those with depressed LV ejection fraction. Its presence varies with not only the methods of assessment, but also characteristics of the study population including the QRS duration, loading condition, severity of coronary artery disease, LV hypertrophy, and LV remodelling. Therefore, the ECG criteria of QRS width ≥ 120 ms adopted in the current guidelines may not be optimal for identifying patients who will benefit most from CRT or defining the presence of mechanical dyssynchrony.6

Analysis of LV dyssynchrony is achieved by different imaging modalities such as echocardiography, from conventional M-mode and Doppler echocardiography to more advanced tissue Doppler imaging (TDI), three-dimensional echocardiography, and speckle tracking imaging, and most of the time, performed at rest. Consequently, lack of mechanical dyssynchrony has been found in about one-third of heart failure patients with QRS duration ≥ 120 ms. On the other hand, mechanical dyssynchrony occurs in 40–50% of patients with a narrow QRS complex defined as < 120 ms.7 Furthermore, numerous studies have suggested that the presence and the extent of LV mechanical dyssynchrony could be a better predictor of response to CRT than QRS duration per se.5,8

Not until recently, the contribution of exercise to LV mechanical dyssynchrony has been investigated and exercise-induced dyssynchrony has been found to be associated with exacerbation of heart failure symptoms, an increase in mitral regurgitation, and a reduction in exercise capacity.2–12 Therefore, it appears that the assessment of LV mechanical dyssynchrony only at rest may not be sufficient in heart failure patients. The landmark study by Lafitte et al.9 first described how mechanical dyssynchrony was modified by exercise in 65 consecutive patients with LV ejection fraction of < 35% and New York Heart Association class II or III symptoms. Depending on the parameter adopted for assessment and using 20% of change as a cut-off point, LV systolic dyssynchrony increased in 28–40%, remained the same in 35–43%, and decreased in 23–31% of the patients during exercise. On a closer inspection, patients could be categorized into four different groups: patients without dyssynchrony at rest but induced by exercise (exercise-induced dyssynchrony), patients with dyssynchrony at rest which normalized during exercise, patients without dyssynchrony at rest as well as during exercise, and patients with dyssynchrony in both situations. The former two groups warranted further investigation to help understand the relationship with lack of response to CRT, which represented 20–26% of the study population. In another study in 60 patients with dilated cardiomyopathy and narrow QRS complex (< 120 ms), significant mechanical dyssynchrony was observed in 33.3% of patients at rest and in 58.3% during exercise. The dynamic change in standard deviations of the time to peak systolic velocity of the 12 LV segments (Ts-SD or Yu Index) as the dyssynchrony measurement between rest and exercise showed an independent positive association with the change in mitral regurgitation, and an independent inverse correlation with the change in LV stroke volume.10 Wang et al.11 reported the occurrence of exercise-evoked systolic dyssynchrony in 11 (33%) of 33 heart failure patients with ejection...
fraction <50%, QRS duration <120 ms, and Ts-SD ≤33 ms, which could be predicted by a higher LV filling pressure at rest. Intriguingly, in the current study by Kühne et al. that enrolled similar patients with symptomatic heart failure and depressed LV ejection fraction who had no dyssynchrony at rest, exercise did not lead to the development of mechanical dyssynchrony in all three groups stratified by QRS duration. Based only on the mean value of dyssynchrony measurement compared at rest and during exercise, the aforementioned conclusion appeared less comprehensive, which could have been interpreted as a ‘false’ neutral effect of exercise on mechanical dyssynchrony as a result of substantial individual variation in dynamic dyssynchrony during exercise, i.e. an increase in dyssynchrony in some participants and a decrease in others. Secondly, subgroup analysis should be interpreted with great caution in a relatively small sample size where group III with QRS duration >150 ms included only six patients.

The relationship between dynamic dyssynchrony and the response to CRT has been explored in several studies. Rocchi et al. in their pioneer study compared the predictive value of dyssynchrony assessed by TDI at rest and during exercise, and found that dyssynchrony during exercise was a better predictor of functional improvement and LV reverse remodelling at 6 months. Recently, Parsai et al. used low-dose dobutamine stress echocardiography (DSE) performed before CRT to assess dynamic dyssynchrony. An early and short-lived septal motion (septal flash), originally as a marker of left bundle branch block-induced dyssynchrony, was adopted to correlate with LV reverse remodeling after CRT. All patients with septal flash at rest showed a significant increase in septal flash excursion at peak stress, which was resolved after CRT, and turned out to be volumetric responders. Furthermore, 5 out of 21 patients (24%) without detectable septal flash at rest who developed a new septal flash during stress also responded to therapy. In the study by Kühne et al., in a subgroup of 15 patients presented with mechanical dyssynchrony at rest who received CRT, all 10 responders had persistent dyssynchrony during exercise, whereas 80% of non-responders showed normalization of dyssynchrony. However, the use of 60% change to define the change in dyssynchrony is arbitrary and the sample size is very small.

Therefore, although the results of these pilot studies may have provided a possible explanation for the lack of response to CRT, the role of assessing exercise or pharmacological-induced dyssynchrony remains to be determined by larger, randomized studies that will compare the response rate to CRT with and without the use of dynamic dyssynchrony. Future studies should further address two issues: whether CRT could potentially be extended to heart failure patients with stress-induced dyssynchrony who do not have dyssynchrony at rest and whether a CRT response rate would be too small in patients with stress-normalized dyssynchrony.

**Conflict of interest: none declared.**

**References**

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